

evaluated a very select group of patients who were monosensitized to birch. Birch allergy in Ligurian patients has been characterized by a relevantly increased prevalence and severity of symptoms.<sup>12</sup> Of interest, patients with the highest degree of birch allergy were IL-17 producers. This finding is particularly relevant considering that the period of observation was outside the pollen season. This phenomenon is not a complete surprise, however, because it might be dependent on a chronic allergic reaction to birch in hypersensitized patients. In this scenario T<sub>H</sub>17 cells are implicated in chronic events of allergic reaction that endure over time.<sup>13</sup> In fact, independent of allergen exposure, IgE production is typically continuous and persistent. Thus IL-17 measurement might define severe immune response, such as that seen in IL-17<sup>+</sup> allergic patients, confirming a previous study that proposed high IL-17 serum levels as a new marker of severity of acute hepatic injury.<sup>6</sup>

On the other hand, this study has some limitations. First, we evaluated a limited number of patients (it is very difficult to enroll monosensitized patients). Second, patients were evaluated only outside the pollen season because all were successively treated with specific immunotherapy. Therefore further studies are required to confirm these preliminary data, mainly concerning the evaluation of patients during the pollen season.

In conclusion, this study provides the first evidence that serum IL-17 levels might be increased in patients monosensitized to birch with the most severe AR. Thus increased IL-17 serum levels can be considered a marker of severe allergy.

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## REFERENCES

- Schmidt-Weber CB, Akdis M, Akdis CA. Th17 cells in the big picture of immunology. *J Allergy Clin Immunol* 2007;120:247-54.
- Hellings PW, Kasran A, Liu Z, Vandekerckhove P, Wuyts A, Overbergh L, et al. IL-17 orchestrates the granulocyte influx into airways after allergen inhalation in a mouse model of allergic asthma. *Am J Respir Cell Mol Biol* 2003;28:42-50.
- Sergejeva S, Ivanov S, Lotvall J, Linden A. IL-17 as a recruitment and survival factor for airway macrophages in allergic airway inflammation. *Am J Respir Cell Mol Biol* 2005;33:248-53.
- Schneider-Candrian S, Togbe D, Couillin I, Mercier I, Brombacher F, Quesniaux V, et al. IL-17 is a negative regulator of established allergic asthma. *J Exp Med* 2006;203:2715-25.
- Klemens C, Rasp G, Jund F, Hilgert E, Devens C, Pfromm F, et al. Mediators and cytokines in allergic and viral-triggered rhinitis. *Allergy Asthma Proc* 2007;28:434-41.
- Yasumi Y, Takikawa Y, Endo R, Suzuki K. Interleukin-17 as a new marker of severity of acute hepatic injury. *Hepatol Res* 2007;37:248-54.
- Hussein MR, Fathi NA, El-Din AM, Hassan HI, Abdullah F, Al-Hakeem, et al. Alteration of the CD4(+), CD8 (+) T cell subsets, interleukins-1beta, IL-10, IL-17, tumor necrosis factor-alpha and soluble intercellular adhesion molecule-1 in

rheumatoid arthritis and osteoarthritis: preliminary observations. *Pathol Oncol Res* 2008; Apr 8 [epub ahead of print].

- Lucia A, Smith L, Naidoo M, Gonzalez-Freire M, Perez M, Rubio JC, et al. McArdle disease: another systemic low-inflammation disorder? *Neurosci Lett* 2008;431:106-11.
- Lei Z, Liu G, Huang O, Ly M, Zu R, Zhang GM, et al. SCF and IL-31 rather than IL-17 and BAFF are potential indicators in patients with allergic asthma. *Allergy* 2008;63:327-32.
- Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 Update (in collaboration with the World Health Organization, GA2LEN and AllerGen). *Allergy* 2008;63(suppl 86):8-160.
- Dreborg S, Backman A, Basomba A. Skin tests used in type I allergy testing. Position paper. *Allergy* 1989;44(suppl 10):1-59.
- Troise C, Voltolini S, Delbono G, Negrini AC. Allergy to pollens from Betulaceae and Corylaceae in a Mediterranean area (Genoa, Italy)—a ten-year retrospective study. *J Invest Allergol Clin Immunol* 1992;2:313-7.
- Romagnani S. Regulation of the T cell response. *Clin Exp Allergy* 2006;36:1357-66.

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## Association of *IL1RL1*, *IL18R1*, and *IL18RAP* gene cluster polymorphisms with asthma and atopy

To the Editor:

Several genome-wide screens, including our own, have shown strong linkage with asthma, lung function, and atopy on chromosome 2q.<sup>1</sup>

The *IL-1 receptorlike-1* (*IL1RL1*) gene, also known as *ST2*, is a promising candidate gene for asthma and atopy. *IL1RL1* is located on 2q12 and resides in a cluster of IL1 receptor genes (*IL-1 receptor 2* [*IL1R2*], *IL1R1*, *IL1RL2*, *IL1RL1*, *IL-18 receptor 1* [*IL18R1*], *IL-18 receptor accessory protein* [*IL18RAP*]).<sup>2</sup>

*IL1RL1*, a member of the Toll-IL-1 receptor superfamily, is a receptor located on mast cells, T<sub>H</sub>2 cells, regulatory T cells, and macrophages and is also present in serum in a soluble form. *IL1RL1* binds IL-33 and exerts its role through Toll-like receptor pathways. Various forms of *IL1RL1* can either stimulate or inhibit T<sub>H</sub>2 responses.<sup>3-6</sup>

Interestingly, single nucleotide polymorphisms (SNPs) located in the *IL1RL1* gene are associated with atopic dermatitis.<sup>7</sup> The adjacently located family members *IL18R1* and *IL18RAP* may also be important in the development of asthma and atopy. The gene products of both *IL18R1* and *IL18RAP* form the α-chain and β-chain of the IL-18 receptor (IL-18R).<sup>8</sup> IL-18R is a key regulator of T<sub>H</sub>1 cells. Binding of IL-18 to IL-18R stimulates T<sub>H</sub>1 cytokine release, but also T<sub>H</sub>2-type cytokines, depending on its cytokine milieu.<sup>9</sup> A recent publication showed strong associations with SNPs located in *IL18R1* and asthma and atopic phenotypes.<sup>10</sup>

Our aim was to investigate whether SNPs in the *IL1RL1* gene are associated with asthma, atopy, and allergic rhinitis. Given the strong linkage disequilibrium (LD) in this region, we also investigated the adjacently located family members *IL18R1* and *IL18RAP*. We analyzed 200 well-characterized Dutch asthma families (n = 1259) with an asthma proband and used 407 independent asthma trios and 226 rhinitis trios to replicate our results. Furthermore, we performed a combined analysis of asthma families and trios to increase power. The medical ethics committee of the University Medical Center Groningen approved all studies, and all participants signed written informed (parental) consent. Families were assessed as described previously.<sup>11</sup> The trios

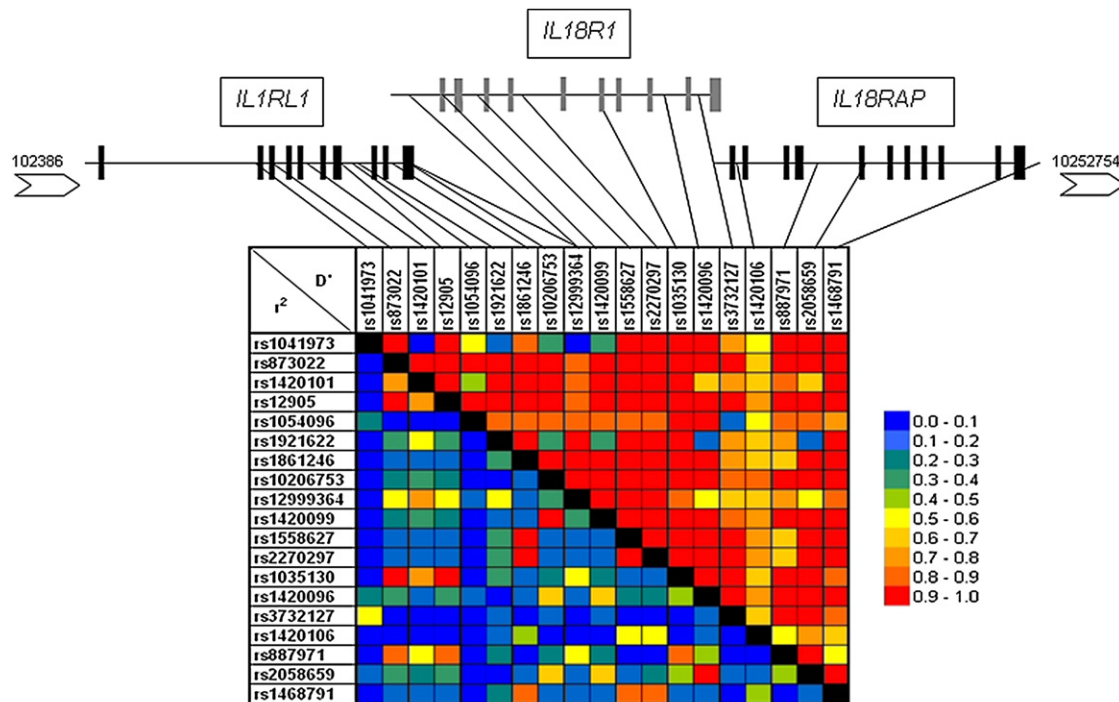


**FIG 1.** SNPs genotyped in *IL1RL1*, *IL18R1*, and *IL18RAP* genes. LD structure ( $r^2$  below and  $D'$  above the diagonal) in the asthma families.

were characterized using the standardized protocol similar to that used in the family study. Bronchial hyperresponsiveness (BHR) to histamine was measured as described previously.<sup>11</sup> BHR was defined as a  $PC_{20} \leq 32$  mg/mL (30 seconds inhalation). Intracutaneous skin testing was performed with 16 (for the families) and 12 (for the trios) common aeroallergens. Asthma was defined by a previously published algorithm.<sup>11</sup>

Twenty-one SNPs located in *IL1RL1*, *IL18R1*, and *IL18RAP* were genotyped. SNPs were selected from the Celera database (<http://www.celeraadiscoverysystem.com>; Celera, Alameda, Calif), and primers were ordered through assay by design service (Applied Biosystems, Foster City, Calif). SNP selection was based on minor allele frequency >10% and location. Whenever possible, the SNPs were located in coding regions with  $\approx 5$  kb distance between each other. Eleven selected SNPs are present in the HapMap database (release 22, April 2007),<sup>12</sup> of which 7 were haplotype tagging SNPs capturing  $\approx 75\%$  of SNPs located in the *IL1RL1*, *IL18R1*, and *IL18RAP* gene cluster.

PCR was performed by using an ABI Prism 9700 HT real-time thermal cycler (Applied Biosystems).

In-house software was used to test for LD ( $D'$  and  $r^2$ ) between the SNPs. Family-Based Association Tests (version 2.0.2) analyses were used for investigation of preferential transmission of alleles ([www.biostat.harvard.edu](http://www.biostat.harvard.edu)).<sup>13</sup> Sliding window analysis with 3 consecutive SNPs was used with Haplotype-Based Association Tests.<sup>12</sup> Results were considered significant if  $P < .05$ .

Family and trio characteristics are shown in this article's Table E1 in the Online Repository at [www.jacionline.org](http://www.jacionline.org). All SNPs were in Hardy-Weinberg equilibrium ( $P > .01$ ). Minor allele frequencies within the asthma families, asthma trios, and rhinitis trios were similar (see this article's Table E2 in the Online Repository at [www.jacionline.org](http://www.jacionline.org)). Genotyping of 2 of 21 SNPs failed because of design problems. Strong LD

between the SNPs was present in all 3 populations (eg, asthma families; Fig 1).

**Asthma families:** Eight of 19 SNPs located in the *IL1RL1*, *IL18R1*, and *IL18RAP* genes were strongly associated with BHR, severity of BHR, and total serum IgE (Table I and Tables E3, E4, and E6 in the Online Repository at [www.jacionline.org](http://www.jacionline.org)). SNPs located in *IL18R1* and *IL18RAP* were also associated with serum eosinophils (see this article's Table E7 in the Online Repository at [www.jacionline.org](http://www.jacionline.org)). Haplotype analysis using sliding windows of 3 consecutive SNPs in all 3 genes showed even stronger associations (asthma,  $P = .003-.05$ ; BHR,  $P = .005-.05$ ; severity of BHR,  $P = .0003-.05$ ; IgE,  $P = .03-.05$ ; and serum eosinophils,  $P = .03-.05$ ).

**Asthma trios:** Significant associations were observed with total serum IgE, serum eosinophils, and skin test positivity and 2 SNPs located in the *IL1RL1* and *IL18R1* gene (Table I and Tables E6-E8). Haplotype analysis showed the associations to be present with SNPs located in the *IL1RL1* and *IL18R1* gene with total IgE ( $P = .03-.05$ ), serum eosinophils ( $P = .04-.05$ ), and skin test positivity ( $P = .02-.05$ ). Three haplotype combinations, [rs1921622, rs1861246, and rs10206753], [rs10206753, rs12999364, and rs1420099], and [rs1420099, rs1558627, and rs2270297], strictly replicated results in the asthma families with similar (borderline) associations with BHR, asthma, and total IgE (Table I) and serum eosinophils ( $P = .03-.06$ ).

**Asthma families and asthma trios combined:** Combination of asthma families and trios resulted in similar or more significant results (Table I and Tables E3-E8). Interestingly, significant associations between asthma and SNPs located in *IL1RL1* and *IL18R1* were found that were not present when analyzing the both cohorts separately (Tables I and E5). Also, haplotype analysis showed a more significant association with asthma ( $P = .0008-.05$ ), BHR ( $P = .0009-.05$ ), BHR severity ( $P = .0006-.05$ ), total

**TABLE I.** Family-Based Association Test of *IL1RL1*, *IL18R1*, and *IL18RAP* with BHR, asthma, and total IgE in the separate and combined analysis of Dutch asthma families and asthma trios

| Analysis of Dutch asthma families and asthma trios |                                   |         |                 |              |                                    |               |
|----------------------------------------------------|-----------------------------------|---------|-----------------|--------------|------------------------------------|---------------|
| Gene                                               | rs No.                            | Allele* | Asthma families | Asthma trios | Asthma families and trios combined |               |
|                                                    |                                   |         | z (P values)    | z (P values) | Informative families               | z (P values)  |
| BHR                                                |                                   |         |                 |              |                                    |               |
| IL1RL1                                             | rs1420101                         | 2       | 1.311 (.190)    | 1.474 (.141) | 211                                | 1.927 (.054)  |
|                                                    | rs1921622                         | 1       | 2.067 (.039)    | 1.432 (.152) | 212                                | 2.463 (.014)  |
|                                                    | rs1861246                         | 1       | 1.969 (.049)    | 1.292 (.196) | 175                                | 2.314 (.021)  |
| IL1RL1 /IL18R1                                     | rs12999364                        | 2       | 1.660 (.097)    | 1.777 (.076) | 198                                | 2.402 (.016)  |
| IL18R1                                             | rs1558627                         | 1       | 2.291 (.022)    | 0.526 (.599) | 180                                | 1.973 (.049)  |
|                                                    | rs2270297                         | 1       | 2.208 (.027)    | 0.590 (.555) | 185                                | 1.975 (.048)  |
|                                                    | rs1035130                         | 2       | 1.496 (.142)    | 1.273 (.203) | 174                                | 1.981 (.048)  |
| IL18RAP                                            | rs1420106                         | 1       | 2.418 (.016)    | 0.813 (.416) | 184                                | 2.277 (.023)  |
| Intergenic                                         | rs1468791                         | 1       | 2.376 (.018)    | 0.221 (.825) | 188                                | 1.816 (.069)  |
| Haplotype                                          |                                   |         |                 |              |                                    |               |
| IL1RL1                                             | rs1921622, rs1861246, rs10206753  | 111     | 2.803 (.005)    | 1.844 (.065) | 192                                | 3.311 (.0009) |
| IL1RL1 /IL18R1                                     | rs10206753, rs12999364, rs1420099 | 121     | 2.125 (.033)    | 1.800 (.072) | 179                                | 2.770 (.006)  |
| Asthma†                                            |                                   |         |                 |              |                                    |               |
| Allele                                             |                                   |         |                 |              |                                    |               |
| IL1RL1                                             | rs1921622                         | 1       | 1.508 (.132)    | 1.451 (.147) | 193                                | 2.074 (.038)  |
|                                                    | rs1861246                         | 1       | 1.201 (.230)    | 1.552 (.121) | 163                                | 1.952 (.050)  |
| IL1RL1 /IL18R1                                     | rs12999364                        | 2       | 1.702 (.089)    | 1.622 (.105) | 185                                | 2.312 (.021)  |
| IL18R1                                             | rs1035130                         | 2       | 1.547 (.122)    | 1.205 (.228) | 159                                | 1.996 (.046)  |
| Haplotype                                          |                                   |         |                 |              |                                    |               |
| IL1RL1                                             | rs1921622, rs1861246, rs10206753  | 111     | 3.020 (.003)    | 1.766 (.077) | 170                                | 3.354 (.0008) |
| IL18R1                                             | rs1420099, rs1558627, rs2270297   | 111     | 2.749 (.006)    | 1.694 (.090) | 180                                | 3.086 (.002)  |
| Total IgE                                          |                                   |         |                 |              |                                    |               |
| Allele                                             |                                   |         |                 |              |                                    |               |
| IL1RL1                                             | rs1054096                         | 2       | −0.971 (.331)   | 1.998 (.046) | 127                                | 0.246 (.806)  |
|                                                    | rs1921622                         | 1       | 1.729 (.084)    | 1.335 (.182) | 276                                | 2.207 (.027)  |
|                                                    | rs1861246                         | 1       | 2.069 (.039)    | 1.070 (.285) | 230                                | 2.320 (.020)  |
| IL18R1                                             | rs1558627                         | 1       | 2.554 (.011)    | 0.229 (.819) | 238                                | 2.203 (.028)  |
|                                                    | rs2270297                         | 1       | 2.142 (.032)    | 0.364 (.716) | 239                                | 1.930 (.054)  |
| IL18RAP                                            | rs1420106                         | 1       | 2.659 (.008)    | 0.554 (.579) | 234                                | 2.516 (.012)  |
| Intergenic                                         | rs1468791                         | 1       | 2.118 (.034)    | 0.257 (.797) | 243                                | 1.833 (.067)  |
| Haplotype                                          |                                   |         |                 |              |                                    |               |
| IL1RL1                                             | rs1921622, rs1861246, rs10206753  | 111     | 1.988 (.046)    | 1.888 (.059) | 245                                | 2.719 (.007)  |

Significant SNP results and consistent haplotype results are shown. z Scores and (uncorrected) P values are shown for the asthma families and asthma trios. Numbers of informative families, z scores, and P values are shown for the combined analysis.

\*Allele 1, major allele; 2, minor allele.

†Asthma based on algorithm.

IgE ( $P = .007-.05$ ), and serum eosinophils ( $P = .005-.05$ ) in all 3 genes, compared with the analysis of both cohorts separately.

Rhinitis trios: No significant associations were found with SNPs located in the *IL1RL1* and *IL18R1* gene and atopic phenotypes in the rhinitis trios (data not shown).

This is the first study that provides suggestive evidence for associations of SNPs in the *IL1RL1* gene and adjacently located family members *IL18R1* and *IL18RAP* with asthma and atopy in 2 independent Dutch asthma populations, but not with rhinitis. This study thus shows the importance of analyzing SNPs in adjacently located genes because it is not decisive whether the associations are caused by the *IL1RL1*, *IL18R1*, and/or *IL18RAP* gene as a result of strong LD in the region.

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## REFERENCES

1. Koppelman GH, Stine OC, Xu J, Howard TD, Zheng SL, Kauffman HF, et al. Genome-wide search for atopy susceptibility genes in Dutch families with asthma. *J Allergy Clin Immunol* 2002;109:498-506.
2. Dale M, Nicklin MJ. Interleukin-1 receptor cluster: gene organization of IL1R2, IL1R1, IL1RL2 (IL-1Rp2), IL1RL1 (T1/ST2), and IL18R1 (IL-1Rp) on human chromosome 2q. *Genomics* 1999;57:177-9.

3. Brint EK, Xu D, Liu H, Dunne A, McKenzie AN, O'Neill LA, et al. ST2 is an inhibitor of interleukin 1 receptor and Toll-like receptor 4 signaling and maintains endotoxin tolerance. *Nat Immunol* 2004;5:373-9.
4. Mangan NE, Dasvarma A, McKenzie AN, Fallon PG. T1/ST2 expression on Th2 cells negatively regulates allergic pulmonary inflammation. *Eur J Immunol* 2007;37:1302-12.
5. Schmitz J, Owyang A, Oldham E, Song Y, Murphy E, McClanahan TK, et al. IL-33, an interleukin-1-like cytokine that signals via the IL-1 receptor-related protein ST2 and induces T helper type 2-associated cytokines. *Immunity* 2005;23:479-90.
6. Hayakawa H, Hayakawa M, Kume A, Tominaga S. Soluble ST2 blocks interleukin-33 signaling in allergic airway inflammation. *J Biol Chem* 2007;282:26369-80.
7. Shimizu M, Matsuda A, Yanagisawa K, Hirota T, Akahoshi M, Inomata N, et al. Functional SNPs in the distal promoter of the ST2 gene are associated with atopic dermatitis. *Hum Mol Genet* 2005;14:2919-27.
8. Torigoe K, Ushio S, Okura T, Kobayashi S, Taniiai M, Kunikata T, et al. Purification and characterization of the human interleukin-18 receptor. *J Biol Chem* 1997;272:25737-42.
9. Nakanishi K, Yoshimoto T, Tsutsui H, Okamura H. Interleukin-18 is a unique cytokine that stimulates both Th1 and Th2 responses depending on its cytokine milieu. *Cytokine Growth Factor Rev* 2001;12:53-72.
10. Zhu G, Whyte MK, Vestbo J, Carlsen K, Carlsen KH, Lenney W, et al. Interleukin 18 receptor 1 gene polymorphisms are associated with asthma. *Eur J Hum Genet* 2008; Apr 2 [epub ahead of print].
11. Panhuysen CI, Bleeker ER, Koeter GH, Meyers DA, Postma DS. Characterization of obstructive airway disease in family members of probands with asthma: an algorithm for the diagnosis of asthma. *Am J Respir Crit Care Med* 1998;157:1734-42.
12. The International HapMap Consortium. The International HapMap Project. *Nature* 2003;426:789-96.
13. Laird NM, Horvath S, Xu X. Implementing a unified approach to family-based tests of association. *Genet Epidemiol* 2000;19(suppl 1):S36-S42.

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## Evaluation of 2 interactive voice-response telephone versions of health-related quality-of-life questionnaires

### To the Editor:

The Standardised Asthma Quality of Life Questionnaire [AQLQ(S)]<sup>1</sup> and the Mini Rhinoconjunctivitis Quality of Life Questionnaire (MiniRQLQ)<sup>2</sup> measure functional problems that patients with these conditions experience in their daily lives. They were developed and validated in paper format. Electronic methods of data collection, including interactive voice-response (IVR) telephone calls, are being used increasingly. We tested the validity of 2 different IVR systems by comparing them with paper questionnaires (the gold standard).

The questionnaires were adapted by 2 well-established and experienced IVR companies [AQLQ(S) in Europe and MiniRQLQ in the United States] who worked closely with the developer (EFJ) on the scripts. All questions have a choice of 7 responses (number and verbal descriptor). These are too complicated to present by telephone and were given to patients on a card before the telephone call. Both systems were pretested in patients for ease of use and accuracy of understanding (cognitive debriefing).

For the AQLQ(S) validation study, adults (age range, 17-65 years) with moderate-to-severe symptomatic asthma were enrolled at the screening visit of a clinical trial (Germany and Italy). They completed the paper version in the morning at the clinic and the IVR call the same evening (usually at home). For the MiniRQLQ study, English-speaking adults (age range, 18-64 years) with a wide range of rhinoconjunctivitis symptoms were

**TABLE I.** Comparison between IVR and paper versions of the AQLQ(S) (n = 54)

|                 | IVR,<br>mean $\pm$<br>SD | Paper,<br>mean $\pm$<br>SD | Paired<br>t test,<br>Difference | P value | Intraclass<br>correlation<br>coefficient |
|-----------------|--------------------------|----------------------------|---------------------------------|---------|------------------------------------------|
| AQLQ(S) overall | 4.18<br>1.27             | 4.07<br>1.36               | 0.11                            | .08     | 0.94                                     |
| Symptoms        | 4.02<br>1.44             | 3.95<br>1.48               | 0.07                            | .43     | 0.90                                     |
| Activities      | 4.24<br>1.35             | 4.27<br>1.48               | -0.03                           | .65     | 0.92                                     |
| Emotions        | 4.27<br>1.47             | 4.02<br>1.53               | 0.25                            | .007    | 0.89                                     |
| Environment     | 4.39<br>1.33             | 3.95<br>1.37               | 0.44                            | <.001   | 0.76                                     |

Higher scores represent better quality of life.

enrolled from patients attending the Allergy Clinic at Kaiser Permanente in San Diego, California. They completed the IVR version at home during the 24 hours before completing the paper version in the clinic. Patients who reported that their symptoms had not changed between completions were included in the analysis. Both studies were approved by local institutional review boards (ethics committees), and all participants signed an informed consent form.

Concordance (agreement plus bias) between paper and IVR scores was examined with an intraclass correlation coefficient (ICC). Bias (consistent difference in one direction) between the 2 methods was examined by using a paired *t* test. We defined *a priori* that validity of the IVR versions would be shown if concordance for the overall score was greater than 0.95 (ICC). This value is slightly lower than the test-retest reproducibility of the paper versions of these questionnaires completed 1 week apart<sup>1,2</sup> and in keeping with the concordance observed in previous validation studies of electronic versions of these questionnaires.<sup>3,4</sup>

AQLQ(S) scores are shown in Table I. The ICC for the overall score of 0.94 did not quite meet the *a priori* defined level of concordance. Of greater concern was bias, with patients tending to record a worse quality of life (lower score) using paper questionnaires compared with IVR questionnaires. Although the overall score did not quite reach significance ( $P = .08$ ), the emotional function and environmental stimuli domains both did ( $P = .007$  and  $P \leq .001$ , respectively). The MiniRQLQ scores are shown in Table II. Not only did the overall concordance (ICC = 0.92) fail to reach the required concordance, there was significant bias, with patients scoring a worse quality of life (higher score) on IVR questionnaires than on paper questionnaires ( $P = .01$ ).

These were the first IVR versions of either questionnaire, and the results suggest that even with careful scripting and cognitive debriefing, there was inadequate concordance between paper and IVR versions to support the validity of these IVR versions. The biases suggest that patients respond differently to paper and IVR questionnaires, but the reason for this is unclear. In both studies the version completed first showed a poorer quality-of-life score, but this is unlikely to be due to a learning effect because numerous test-retest studies on paper questionnaires have shown that this does not occur. In addition, differences only occurred in some domains. With the paper versions being completed in the clinic

**TABLE E1.** Clinical characteristics of Dutch families from probands with asthma

|                                              | Probands         | Spouses          | Children        | Grandchildren   |
|----------------------------------------------|------------------|------------------|-----------------|-----------------|
| No. (% female)                               | 200 (38)         | 201* (62)        | 556 (54)        | 194 (51)        |
| Age (y), median (range)                      | 52.5 (37.8-75.3) | 51.5 (33.1-76.5) | 24.5 (6.8-53.4) | 12.7 (4.6-41.8) |
| Asthma (%)                                   | 91               | 10.6             | 31.4            | 39.6            |
| BHR (%)                                      | 100              | 25.6             | 45.3            | 59.8            |
| Total IgE (IU/mL),<br>geometric mean (range) | 92.9 (1.0-2880)  | 26.2 (0.5-1940)  | 63.5 (0.5-3360) | 63.8 (0.5-3710) |
| Positive skin tests (%)                      | 82.8             | 31.0             | 53.3            | 32.8            |
| Blood eosinophils 10E7,<br>mean (range)      | 15.8 (0-126.5)   | 9.4 (0-63.8)     | 15.8 (0-294.8)  | 20.5 (0-177)    |

| Clinical characteristics of probands of asthma and rhinitis trios | Asthma probands   | Rhinitis probands |
|-------------------------------------------------------------------|-------------------|-------------------|
| No. (% female)                                                    | 407 (63.1)        | 226 (56.2)        |
| Age (y), median (range)                                           | 34.3 (18.1-64.7)  | 32.5 (18-46.7)    |
| Asthma (%)                                                        | 86.9              | 15.3              |
| BHR (%)                                                           | 91                | 33                |
| Total IgE (IU/mL), geometric mean (range)                         | 108.5 (0.5-12400) | 115.7 (5-6915)    |
| Positive skin tests (%)                                           | 82.9              | 95.5              |
| Blood eosinophils 10E7, mean (range)                              | 16.5 (1.0-94)     | 16.3 (1.0-78)     |

\*One proband married twice; both spouses participated in the study.

**TABLE E2.** SNPs selected for *IL1RL1*, *IL18R1* and *IL18RAP* in Dutch asthma family study, asthma trios and rhinitis trios

| Gene                  | Rs no.     | Function       | Allele* | Minor allele frequency |              |                |
|-----------------------|------------|----------------|---------|------------------------|--------------|----------------|
|                       |            |                |         | Asthma families        | Asthma trios | Rhinitis trios |
| <i>IL1RL1</i>         | rs1041973  | Missense       | C/A     | 0.15                   | 0.18         | 0.19           |
| <i>IL1RL1</i>         | rs873022   | Intron         | G/T     | 0.33                   | 0.29         | 0.29           |
| <i>IL1RL1</i>         | rs1420101  | Intron/silent  | G/A     | 0.38                   | 0.35         | 0.36           |
| <i>IL1RL1</i>         | rs12905    | 3'UTR/intron   | G/A     | 0.32                   | 0.29         | 0.29           |
| <i>IL1RL1</i>         | rs1054096  | Intron         | T/C     | 0.08                   | 0.09         | 0.11           |
| <i>IL1RL1</i>         | rs1921622  | Intron         | A/G     | 0.46                   | 0.46         | 0.46           |
| <i>IL1RL1</i>         | rs1861246  | Intron         | C/T     | 0.22                   | 0.24         | 0.23           |
| <i>IL1RL1</i>         | rs10206753 | Missense       | T/C     | 0.38                   | 0.39         | 0.38           |
| <i>IL1RL1 /IL18R1</i> | rs12999364 | 3'UTR/promoter | C/T     | 0.36                   | 0.38         | 0.39           |
| <i>IL18R1</i>         | rs1420099  | Intron         | C/G     | 0.38                   | 0.38         | 0.38           |
| <i>IL18R1</i>         | rs1558627  | Intron         | A/G     | 0.22                   | 0.25         | 0.23           |
| <i>IL18R1</i>         | rs2270297  | Intron         | C/T     | 0.23                   | 0.25         | NG             |
| <i>IL18R1</i>         | rs1035130  | Missense       | A/G     | 0.33                   | 0.29         | 0.29           |
| <i>IL18R1</i>         | rs1420096  | Intron         | C/T     | 0.47                   | 0.46         | NG             |
| <i>IL18R1</i>         | rs3732127  | 3'UTR          | G/C     | 0.13                   | 0.13         | NG             |
| <i>IL18RAP</i>        | rs1420106  | Promoter       | G/A     | 0.22                   | 0.25         | NG             |
| <i>IL18RAP</i>        | rs887971   | Intron         | T/C     | 0.32                   | 0.33         | NG             |
| <i>IL18RAP</i>        | rs2058659  | Intron         | G/A     | 0.48                   | 0.45         | NG             |
| Intergenic            | rs1468791  | Intergenic     | G/A     | 0.22                   | 0.25         | NG             |

NG, Not genotyped; UTR, untranslated region.

\*Major allele first.

**TABLE E3.** Family-Based Association Test of *IL1RL1*, *IL18R1*, and *IL18RAP* with BHR in the separate and combined analysis of Dutch asthma families and asthma trios

| Gene                  | Rs no.     | Allele | BHR                         |                             |                                    |                             |
|-----------------------|------------|--------|-----------------------------|-----------------------------|------------------------------------|-----------------------------|
|                       |            |        | Families                    | Trios                       | Asthma families and trios combined |                             |
|                       |            |        | <i>z</i> ( <i>P</i> values) | <i>z</i> ( <i>P</i> values) | Informative families               | <i>z</i> ( <i>P</i> values) |
| <i>IL1RL1</i>         | rs1041973  | 1      | 0.028 (.978)                | 0.266 (.790)                | 154                                | 0.212 (.831)                |
|                       | rs873022   | 2      | 1.204 (.229)                | 0.587 (.557)                | 197                                | 1.297 (.194)                |
|                       | rs1420101  | 2      | 1.311 (.190)                | 1.474 (.141)                | 211                                | 1.927 (.054)                |
|                       | rs12905    | 2      | 1.513 (.130)                | 0.899 (.368)                | 190                                | 1.741 (.082)                |
|                       | rs1054096  | 2      | 0.186 (.852)                | 1.395 (.163)                | 91                                 | 1.016 (.310)                |
|                       | rs1921622  | 1      | 2.067 (.039)                | 1.432 (.152)                | 212                                | 2.463 (.014)                |
|                       | rs1861246  | 1      | 1.969 (.049)                | 1.292 (.196)                | 175                                | 2.314 (.021)                |
|                       | rs10206753 | 1      | 0.337 (.736)                | 1.237 (.216)                | 214                                | 1.044 (.297)                |
| <i>IL1RL1 /IL18R1</i> | rs12999364 | 2      | 1.660 (.097)                | 1.777 (.076)                | 198                                | 2.402 (.016)                |
| <i>IL18R1</i>         | rs1420099  | 1      | 0.335 (.738)                | 1.504 (.133)                | 214                                | 1.210 (.226)                |
|                       | rs1558627  | 1      | 2.291 (.022)                | 0.526 (.599)                | 180                                | 1.973 (.049)                |
|                       | rs2270297  | 1      | 2.208 (.027)                | 0.590 (.555)                | 185                                | 1.975 (.048)                |
|                       | rs1035130  | 2      | 1.496 (.142)                | 1.273 (.203)                | 174                                | 1.981 (.048)                |
|                       | rs1420096  | 1      | −0.302 (.763)               | 0.469 (.639)                | 227                                | 0.072 (.942)                |
|                       | rs3732127  | 1      | −0.043 (.966)               | 0.749 (.454)                | 126                                | 0.596 (.551)                |
| <i>IL18RAP</i>        | rs1420106  | 1      | 2.418 (.016)                | 0.813 (.416)                | 184                                | 2.277 (.023)                |
|                       | rs887971   | 2      | 0.795 (.427)                | 0.840 (.401)                | 205                                | 1.157 (.247)                |
|                       | rs2058659  | 1      | −0.217 (.828)               | 0.668 (.504)                | 233                                | 0.281 (.777)                |
| Intergenic            | rs1468791  | 1      | 2.376 (.018)                | 0.221 (.825)                | 188                                | 1.816 (.069)                |

*z* Scores and (uncorrected) *P* values are shown for the asthma families and asthma trios. Numbers of informative families, *z* scores, and *P* values are shown for the combined analysis.

**TABLE E4.** Family-Based Association Test of *IL1RL1*, *IL18R1*, and *IL18RAP* with BHR severity in the separate and combined analysis of Dutch asthma families and asthma trios

| Gene                  | Rs no.     | Allele | BHR severity                |                             |                                    |                             |
|-----------------------|------------|--------|-----------------------------|-----------------------------|------------------------------------|-----------------------------|
|                       |            |        | Families                    | Trios                       | Asthma families and trios combined |                             |
|                       |            |        | <i>z</i> ( <i>P</i> values) | <i>z</i> ( <i>P</i> values) | Informative families               | <i>z</i> ( <i>P</i> values) |
| <i>IL1RL1</i>         | rs1041973  | 2      | 0.703 (.482)                | −0.184 (.854)               | 160                                | 0.446 (.656)                |
|                       | rs873022   | 2      | 1.637 (.101)                | 0.106 (.916)                | 198                                | 1.413 (.158)                |
|                       | rs1420101  | 2      | 2.145 (.032)                | −0.028 (.978)               | 213                                | 1.79 (.073)                 |
|                       | rs12905    | 2      | 1.742 (.082)                | 0.228 (.819)                | 192                                | 1.578 (.114)                |
|                       | rs1054096  | 2      | 1.693 (.090)                | 0.032 (.974)                | 101                                | 1.512 (.131)                |
|                       | rs1921622  | 1      | 2.637 (.008)                | −0.246 (.806)               | 214                                | 1.979 (.048)                |
|                       | rs1861246  | 1      | 2.235 (.025)                | 1.113 (.266)                | 176                                | 2.420 (.016)                |
|                       | rs10206753 | 1      | 1.045 (.296)                | 0.241 (.810)                | 208                                | 1.032 (.301)                |
| <i>IL1RL1 /IL18R1</i> | rs12999364 | 2      | 3.150 (.002)                | 0.142 (.887)                | 203                                | 2.640 (.008)                |
| <i>IL18R1</i>         | rs1420099  | 1      | 1.004 (.315)                | −0.106 (.916)               | 210                                | 0.827 (.409)                |
|                       | rs1558627  | 1      | 2.631 (.009)                | −0.199 (.841)               | 180                                | 1.881 (.060)                |
|                       | rs2270297  | 1      | 2.442 (.015)                | 0.083 (.934)                | 183                                | 1.925 (.054)                |
|                       | rs1035130  | 2      | 1.836 (.066)                | 0.376 (.707)                | 176                                | 1.747 (.081)                |
|                       | rs1420096  | 2      | 0.272 (.785)                | −0.149 (.881)               | 221                                | 0.152 (.880)                |
|                       | rs3732127  | 2      | 0.926 (.355)                | 0.227 (.821)                | 127                                | 0.851 (.395)                |
| <i>IL18RAP</i>        | rs1420106  | 1      | 2.633 (.008)                | −0.006 (.995)               | 181                                | 2.000 (.045)                |
|                       | rs887971   | 2      | 1.494 (.135)                | −0.334 (.739)               | 204                                | 1.010 (.312)                |
|                       | rs2058659  | 2      | 0.196 (.844)                | −0.028 (.978)               | 226                                | 0.151 (.880)                |
| Intergenic            | rs1468791  | 1      | 2.673 (.008)                | −0.224 (.823)               | 184                                | 1.887 (.059)                |

*z* Scores and (uncorrected) *P* values are shown for the asthma families and asthma trios. Numbers of informative families, *z* scores, and *P* values are shown for the combined analysis.

**TABLE E5.** Family-Based Association Test of *IL1RL1*, *IL18R1*, and *IL18RAP* with asthma in the separate and combined analysis of Dutch asthma families and asthma trios

| Gene                  | Rs no.     | Allele | Asthma*       |               |                                    |              |
|-----------------------|------------|--------|---------------|---------------|------------------------------------|--------------|
|                       |            |        | Families      | Trios         | Asthma families and trios combined |              |
|                       |            |        | z (P values)  | z (P values)  | Informative families               | z (P values) |
| <i>IL1RL1</i>         | rs1041973  | 2      | 0.020 (.984)  | 0.092 (.926)  | 139                                | 0.083 (.934) |
|                       | rs873022   | 2      | 1.382 (.167)  | 0.300 (.764)  | 178                                | 1.201 (.230) |
|                       | rs1420101  | 2      | 1.816 (.069)  | 1.155 (.248)  | 196                                | 2.063 (.039) |
|                       | rs12905    | 2      | 1.460 (.144)  | 0.688 (.491)  | 171                                | 1.540 (.124) |
|                       | rs1054096  | 2      | 0.000 (1.000) | 1.612 (.107)  | 79                                 | 1.212 (.225) |
|                       | rs1921622  | 1      | 1.508 (.132)  | 1.451 (.147)  | 193                                | 2.074 (.038) |
|                       | rs1861246  | 1      | 1.201 (.230)  | 1.552 (.121)  | 163                                | 1.952 (.050) |
|                       | rs10206753 | 1      | 1.397 (.162)  | 0.827 (.408)  | 190                                | 1.575 (.115) |
| <i>IL1RL1 /IL18R1</i> | rs12999364 | 2      | 1.702 (.089)  | 1.622 (.105)  | 185                                | 2.312 (.021) |
| <i>IL18R1</i>         | rs1420099  | 1      | 1.479 (.139)  | 1.109 (.268)  | 190                                | 1.823 (.068) |
|                       | rs1558627  | 1      | 1.387 (.166)  | 0.846 (.397)  | 164                                | 1.527 (.127) |
|                       | rs2270297  | 1      | 1.309 (.191)  | 0.905 (.366)  | 171                                | 1.536 (.125) |
|                       | rs1035130  | 2      | 1.547 (.122)  | 1.205 (.228)  | 159                                | 1.996 (.046) |
|                       | rs1420096  | 1      | 0.381 (.703)  | 0.000 (1.000) | 201                                | 0.266 (.790) |
|                       | rs3732127  | 1      | 1.175 (.240)  | 0.385 (.700)  | 122                                | 1.019 (.308) |
| <i>IL18RAP</i>        | rs1420106  | 1      | 1.427 (.154)  | 1.134 (.257)  | 170                                | 1.796 (.073) |
|                       | rs887971   | 2      | 1.592 (.111)  | 0.641 (.521)  | 185                                | 1.556 (.120) |
|                       | rs2058659  | 1      | 0.892 (.372)  | 0.206 (.837)  | 203                                | 0.762 (.446) |
| Intergenic            | rs1468791  | 1      | 1.180 (.238)  | 0.526 (.599)  | 173                                | 1.169 (.243) |

z Scores and (uncorrected) P values are shown for the asthma families and asthma trios. Numbers of informative families, z scores, and P values are shown for the combined analysis.

\*Asthma based on algorithm.<sup>15</sup>

**TABLE E6.** Family-Based Association Test of *IL1RL1*, *IL18R1*, and *IL18RAP* with total IgE in the separate and combined analysis of Dutch asthma families and asthma trios

| Gene                  | Rs no.     | Allele | Total IgE     |               | Asthma families and trios combined | z (P values) |
|-----------------------|------------|--------|---------------|---------------|------------------------------------|--------------|
|                       |            |        | Families      | Trios         |                                    |              |
|                       |            |        | z (P values)  | z (P values)  | Informative families               |              |
| <i>IL1RL1</i>         | rs1041973  | 2      | 0.343 (.732)  | 0.513 (.879)  | 197                                | 0.364 (.716) |
|                       | rs873022   | 2      | 0.872 (.383)  | 0.396 (.692)  | 265                                | 0.952 (.341) |
|                       | rs1420101  | 2      | 0.840 (.401)  | 1.385 (.166)  | 276                                | 1.469 (.142) |
|                       | rs12905    | 2      | 1.091 (.275)  | 0.891 (.373)  | 255                                | 1.406 (.160) |
|                       | rs1054096  | 2      | −0.971 (.331) | 1.998 (.046)  | 127                                | 0.246 (.806) |
|                       | rs1921622  | 1      | 1.729 (.084)  | 1.335 (.182)  | 276                                | 2.207 (.027) |
|                       | rs1861246  | 1      | 2.069 (.039)  | 1.070 (.285)  | 230                                | 2.320 (.020) |
|                       | rs10206753 | 1      | −0.124 (.901) | 1.351 (.179)  | 274                                | 0.638 (.524) |
| <i>IL1RL1 /IL18R1</i> | rs12999364 | 2      | 0.100 (.920)  | 1.800 (.072)  | 266                                | 1.212 (.226) |
| <i>IL18R1</i>         | rs1420099  | 1      | −0.181 (.856) | 1.743 (.081)  | 274                                | 0.824 (.410) |
|                       | rs1558627  | 1      | 2.554 (.011)  | 0.229 (.819)  | 238                                | 2.203 (.028) |
|                       | rs2270297  | 1      | 2.142 (.032)  | 0.364 (.716)  | 239                                | 1.930 (.054) |
|                       | rs1035130  | 2      | 0.582 (.561)  | 1.131 (.258)  | 240                                | 1.109 (.267) |
|                       | rs1420096  | 2      | 1.062 (.288)  | −0.441 (.659) | 289                                | 0.598 (.550) |
|                       | rs3732127  | 1      | 0.432 (.666)  | 0.760 (.447)  | 158                                | 0.872 (.383) |
| <i>IL18RAP</i>        | rs1420106  | 1      | 2.659 (.008)  | 0.554 (.579)  | 234                                | 2.516 (.012) |
|                       | rs887971   | 2      | −0.018 (.986) | 0.583 (.560)  | 274                                | 0.324 (.746) |
|                       | rs2058659  | 2      | 0.568 (.570)  | −0.675 (.499) | 296                                | 0.057 (.954) |
| Intergenic            | rs1468791  | 1      | 2.118 (.034)  | 0.257 (.797)  | 243                                | 1.833 (.067) |

z Scores and (uncorrected) P values are shown for the asthma families and asthma trios. Numbers of informative families, z scores, and P values are shown for the combined analysis.

**TABLE E7.** Family-Based Association Test of *IL1RL1*, *IL18R1*, and *IL18RAP* with serum eosinophils in the separate and combined analysis of Dutch asthma families and asthma trios

| Gene                  | Rs no.     | Allele | Serum eosinophils           |                             | Asthma families and trios combined |              |
|-----------------------|------------|--------|-----------------------------|-----------------------------|------------------------------------|--------------|
|                       |            |        | Families                    | Trios                       | Informative families               |              |
|                       |            |        | <i>z</i> ( <i>P</i> values) | <i>z</i> ( <i>P</i> values) | <i>z</i> ( <i>P</i> values)        |              |
| <i>IL1RL1</i>         | rs1041973  | 2      | 0.010 (.992)                | 0.298 (.766)                | 190                                | 0.183 (.855) |
|                       | rs873022   | 2      | 0.720 (.471)                | 0.461 (.645)                | 254                                | 0.853 (.394) |
|                       | rs1420101  | 2      | 0.784 (.433)                | 1.379 (.168)                | 267                                | 1.369 (.171) |
|                       | rs12905    | 2      | 0.904 (.366)                | 0.834 (.404)                | 249                                | 1.203 (.229) |
|                       | rs1054096  | 2      | −0.330 (.742)               | 1.791 (.073)                | 125                                | 0.566 (.572) |
|                       | rs1921622  | 1      | 1.512 (.130)                | 1.438 (.150)                | 268                                | 2.040 (.041) |
|                       | rs1861246  | 1      | 1.861 (.063)                | 1.538 (.124)                | 227                                | 2.374 (.018) |
|                       | rs10206753 | 1      | 0.012 (.990)                | 1.226 (.220)                | 266                                | 0.657 (.511) |
| <i>IL1RL1 /IL18R1</i> | rs12999364 | 2      | 0.147 (.883)                | 2.012 (.044)                | 257                                | 1.281 (.200) |
| <i>IL18R1</i>         | rs1420099  | 1      | −0.074 (.941)               | 1.705 (.088)                | 265                                | 0.844 (.399) |
|                       | rs1558627  | 1      | 2.411 (.016)                | 0.640 (.522)                | 235                                | 2.323 (.020) |
|                       | rs2270297  | 1      | 2.086 (.037)                | 0.773 (.440)                | 234                                | 2.127 (.033) |
|                       | rs1035130  | 2      | 0.444 (.657)                | 0.979 (.328)                | 233                                | 0.886 (.376) |
|                       | rs1420096  | 2      | 1.007 (.314)                | −0.155 (.877)               | 279                                | 0.754 (.451) |
|                       | rs3732127  | 1      | 0.661 (.509)                | 0.318 (.750)                | 152                                | 0.717 (.473) |
| <i>IL18RAP</i>        | rs1420106  | 1      | 2.879 (.004)                | 1.081 (.280)                | 230                                | 2.968 (.003) |
|                       | rs887971   | 2      | −0.105 (.916)               | 0.891 (.373)                | 265                                | 0.397 (.691) |
|                       | rs2058659  | 2      | 0.841 (.400)                | −0.343 (.731)               | 286                                | 0.513 (.608) |
| Intergenic            | rs1468791  | 1      | 2.123 (.034)                | 0.684 (.494)                | 239                                | 2.093 (.036) |

*z* Scores and (uncorrected) *P* values are shown for the asthma families and asthma trios. Numbers of informative families, *z* scores, and *P* values are shown for the combined analysis.

**TABLE E8.** Family-Based Association Test of *IL1RL1*, *IL18R1*, and *IL18RAP* with positive skin test result in the separate and combined analysis of Dutch asthma families and asthma trios

| Gene                  | Rs no.     | Allele* | Positive skin test result |               |                                    |              |
|-----------------------|------------|---------|---------------------------|---------------|------------------------------------|--------------|
|                       |            |         | Families                  | Trios         | Asthma families and trios combined |              |
|                       |            |         | z (P values)              | z (P values)  | Informative families               | z (P values) |
| <i>IL1RL1</i>         | rs1041973  | 2       | 0.573 (.567)              | −0.191 (.849) | 137                                | 0.249 (.080) |
|                       | rs873022   | 1       | 0.307 (.759)              | −0.234 (.815) | 192                                | 0.096 (.932) |
|                       | rs1420101  | 2       | −0.176 (.860)             | 1.199 (.230)  | 202                                | 0.584 (.560) |
|                       | rs12905    | 2       | 0.063 (.950)              | 0.318 (.750)  | 184                                | 0.244 (.807) |
|                       | rs1054096  | 2       | −0.863 (.388)             | 2.151 (.031)  | 88                                 | 0.796 (.426) |
|                       | rs1921622  | 1       | 0.000 (1.000)             | 1.474 (.141)  | 205                                | 0.968 (.333) |
|                       | rs1861246  | 1       | 1.020 (.308)              | 0.811 (.417)  | 169                                | 1.273 (.203) |
|                       | rs10206753 | 1       | −0.338 (.735)             | 1.631 (.103)  | 203                                | 0.751 (.452) |
| <i>IL1RL1 /IL18R1</i> | rs12999364 | 2       | −1.121 (.262)             | 1.818 (.069)  | 197                                | 0.321 (.748) |
| <i>IL18R1</i>         | rs1420099  | 1       | −0.283 (.777)             | 1.613 (.107)  | 205                                | 0.798 (.424) |
|                       | rs1558627  | 1       | 1.256 (.209)              | 0.160 (.873)  | 180                                | 1.030 (.303) |
|                       | rs2270297  | 1       | 0.787 (.431)              | 0.157 (.875)  | 182                                | 0.676 (.499) |
|                       | rs1035130  | 2       | −0.512 (.609)             | 0.828 (.408)  | 172                                | 0.102 (.919) |
|                       | rs1420096  | 2       | 1.211 (.226)              | −0.489 (.625) | 217                                | 0.578 (.563) |
|                       | rs3732127  | 1       | −0.388 (.698)             | 1.294 (.196)  | 120                                | 0.699 (.485) |
| <i>IL18RAP</i>        | rs1420106  | 1       | 1.693 (.090)              | 0.552 (.581)  | 174                                | 1.626 (.104) |
|                       | rs887971   | 1       | 0.660 (.509)              | −0.455 (.649) | 194                                | 0.211 (.833) |
|                       | rs2058659  | 2       | 0.668 (.504)              | −0.626 (.532) | 218                                | 0.077 (.939) |
| Intergenic            | rs1468791  | 1       | 1.065 (.287)              | −0.078 (.938) | 183                                | 0.724 (.469) |

z Scores and (uncorrected) P values are shown for the asthma families and asthma trios. Numbers of informative families, z scores, and P values are shown for the combined analysis.

\*Allele 1, major allele; 2, minor allele.